IN THE NEWS

Smoke signals

Smokers die on average 10 years earlier than non-smokers; so concludes a landmark study published in the *British Medical Journal* (26 June 2004). This and other findings of the now-famous prospective study of the long-term smoking habits of over 34,000 British male doctors are the culmination of 50-years research into the effects of cigarette smoking in this cohort.

"Since the study began in 1951, tobacco has killed around 100 million people globally", commented Alex Markham of Cancer Research UK (*http://news.bbc.co.uk*, 25 June 2004). But quantification of the risk of smoking has been limited. The results of this study provide some sobering facts and figures for smokers: "It is clear that consistent cigarette smoking doubles mortality throughout adult life" (*Reuters*, 22 June 2004), remarked Richard Doll, the Oxford University professor who initiated the study and first discovered the link between smoking and lung cancer.

However, the news is not all bad: "... we also know that stopping smoking will significantly limit the harm" (*San Francisco Chronicle*, 23 June 2004), said Richard Peto, Doll's colleague of 30 years on the study. In fact, the study found that stopping smoking at age 50 added 6 years to life expectancy. Furthermore, stopping before the age of 30 avoids almost all hazard associated with smoking.

The study conclusions are stark for those who continue to smoke, but also signal to those who are keen on quitting that it is not too late to do so. As Peto remarked, "Smoking kills people and stopping works" (*Reuters*, 22 June 2004).

Oliver Childs

TUMORIGENESIS

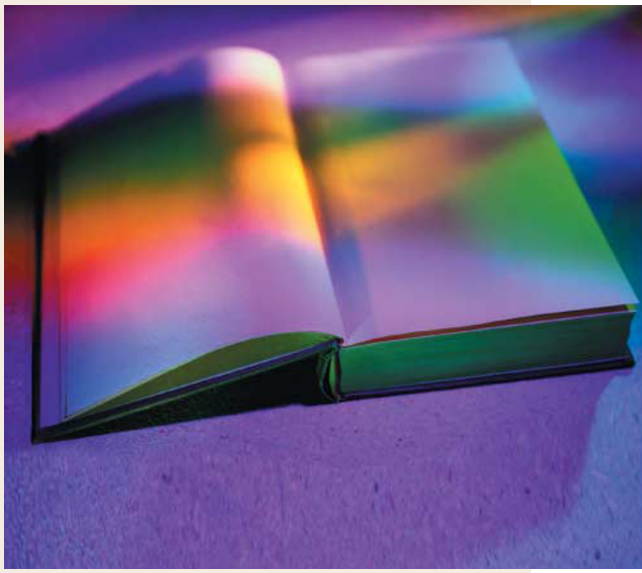
An original beginning

The retinoblastoma tumour suppressor (*RB*) is a key regulator of the cell cycle; its loss prevents cell-cycle arrest and induces apoptosis in many tissues. These findings prompted speculation that the tumour 'cell of origin' for retinoblastoma would be one that has acquired an anti-apoptotic mutation. However, two separate groups have reached the similar and surprising conclusion that, in mice, the cell of origin for this tumour is naturally resistant to the effects of *Rb* loss.

The laboratories of Rod Bremner and Tyler Jacks have closely examined how retinal development is subverted through *Rb* loss, leading to tumour formation. Modelling retinoblastoma in mice is difficult because loss of both *Rb* alleles in all tissues is lethal and $Rb^{+/-}$ mice develop pituitary rather than retinal tumours. Previous evidence from an earlier mouse model implied that the RB-like protein p107 can compensate for *Rb* loss in the retina. So, these two groups have used mice specifically deficient for RB function in the retina and crossed them with mice lacking expression of either of the *Rb*-like genes *p107* or *p130*.

Retinal cells pass through three basic developmental stages — expansion of progenitors, differentiation into seven post-mitotic precursor retinal cell types and terminal differentiation. Bremner and co-workers mapped retinal cell fates in mice with *Rb* function conditionally absent in the progenitor cells of the peripheral retina ($\alpha Cre/Rb^{lox/lox}$) and also crossed these mice with $p107^{-/-}$ mice. The $Rb^{-/-}p107^{-/-}$ mice developed retinoblastoma. Staining for the precursor cell types in the retina of embryonic and neonatal mice showed that all seven cell types were evident, indicating that *Rb* loss does not cause a defect in differentiation. Extensive apoptosis as well as large numbers of S-phase cells were evident in the mutant mice, particularly at developmental time points where terminal differentiation of retinal precursors occurs.

Jacks and co-workers also studied retinas with a conditional *Rb* deletion. In one approach, *Rb* function was disrupted within almost all cells of the retina, nervous system and other tissues (*Rb* mosaics) and these mice were crossed with $p107^{-/-}$ or $p130^{-/-}$ mice. The *Rb* mosaic $p130^{-/-}$ mice developed retinoblastoma with histology very similar to human tumours, indicating that, like p107, p130 might compensate for *Rb* loss in mice. In another approach, Jacks and colleagues used the same $\alpha Cre/Rb^{lox/lox}$ mice as the Bremner lab to accurately determine retinal cell fate in the absence of *Rb* only. They observed similar results to the Bremner lab, concluding that apoptotic and S-phase cells corresponded primarily with terminally differentiating cells. Given that loss of *Rb* predisposes terminally differentiating retinal cells to apoptosis, which cells survive to go on to form tumours?



Both groups found that four terminally differentiated cell types — ganglion, rod, cone and bipolar cells — were lost, whereas some horizontal, Muller glia and amacrine cells survived. The survival of amacrine cells might explain why *Rb* loss leads to amacrine-rich retinoblastomas in $Rb^{-/-}p107^{-/-}$ or $Rb^{-/-}p130^{-/-}$ mice.

But why do amacrine cells survive when other cell types do not? Both research groups conclude that amacrine cells are more resistant to *Rb* loss and can survive the many rounds of replication that result before they terminally differentiate. Therefore, the retinoblastoma cell of origin arises from a pool of intrinsically apoptosis-resistant differentiating precursors with extended, but finite, division capacity. These cells presumably undergo further mutations to evade terminal differentiation. Discovering this particular property of the cell of origin should help identify both further mutations that are involved in the development of human retinoblastoma and novel tumour therapy targets.

Nicola McCarthy

References and links

ORIGINAL RESEARCH PAPERS Chen, D. *et al.* Cell specific effects of RB or RB/p107 loss on retinal development implicate an intrinsically death-resistant cell-of-origin in retinoblastoma. *Cancer Cell* **5**, 539–551 (2004) | MacPherson, D. *et al.* Cell-type specific effects of Rb deletion in the murine retina. *Genes Dev.* 15 July 2004 (doi:10.1101/gad.1203304)

FURTHER READING Zhang, J., Schweers, B. & Dyer, M.A. The first knockout mouse model of retinoblastoma. *Cell Cycle* 7 July 2004 [epub ahead of print]

WEB SITES

Rod Bremner's lab: http://vsrp.uhnres.utoronto.ca/Bremner.html

Tyler Jacks' lab: http://web.mit.edu/biology/www/facultyareas/facresearch/jacks.shtml